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Seroprevalence of SARS-CoV-2 Antibodies in Children- a Prospective Multicentre Cohort Study Protocol

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Abstract

Introduction:

A novel coronavirus SARS-CoV-2 has been responsible for a worldwide pandemic. Children typically have very mild, or no, symptoms of infection. This makes estimations of seroprevalence in children difficult. Research is therefore required to determine the seroprevalence of SARS-CoV-2 antibodies in children and to determine if those antibodies are neutralising antibodies suggestive of immunity. The primary objective of this study is to report the seroprevalence of SARS-CoV-2 Immunoglobulin M (IgM) and/or Immunoglobulin G (IgG) antibodies in healthy children at baseline, two months and six months. This is the only longitudinal UK study of seroprevalence in an exclusively paediatric population. Determining the changing seroprevalence is of vital public health importance and can help inform decisions around the lifting of paediatric specific social distancing measures such as school closures and the cancellation of routine paediatric hospital services.

Methods and Analysis:

1000 healthy children of healthcare workers aged between 2 and 15 years will be recruited from five UK sites (Belfast, Cardiff, Glasgow, London and Manchester). The children will undergo phlebotomy at baseline, 2 months and 6 months to measure IgM and/or IgG positivity to SARS-CoV-2. A sample size of 675 patients is required to detect a 5% change in seroprevalence at each time point assuming an alpha of 0.05 and a beta of 0.2. Adjusted probabilities for the presence of IgG and/or IgM antibodies and of SARS-CoV-2 infection will be reported using logistic regression models where appropriate. Trial Registration: NCT0434740

Ethics and Dissemination:

Ethical approval was obtained from the London - Chelsea Research Ethics Committee (REC Reference - 20/HRA/1731) and the Belfast Health & Social Care Trust Research Governance (Reference 19147TW-SW). Results of this study will be made available as pre-prints and submitted for publication in peer-reviewed journals.

Word Count: 2081

Article Summary

- This study is a large multicentre cohort study concerning the seroprevalence of IgG and/or IgM antibodies to Sars-CoV-2 in children over 6 months.
- This is the only longitudinal UK study of seroprevalence in exclusively paediatric populations, and will provide important information which could help guide public health policy related to the COVID-19 pandemic.
- The geographic spread of sites across all four nations of the UK will provide detail of regional variation of seroprevalence.
- Whilst chosen for practical reasons the inclusion of only children of healthcare workers may limit the generalisability of this study to the whole population.
- A limitation of this study is that it is not powered to detect very small (less than 5%) changes in seroprevalence

Technical summary

Study Title:	The seroprevalence of SARS-CoV-2 antibodies in children - a prospective multicentre cohort study.
Protocol Version:	Version 7.0 (Date 30th May 2020)
Study Registration:	NCT04347408
Study Sponsor:	Queen's University Belfast Sponsors reference IRAS282617 Ms Paula Tighe p.tighe@qub.ac.uk
Steering Committee Members	Dr Thomas Waterfield Dr Sharon Christie Dr Shamez Ladhani Dr Shazaad Ahmad Dr Jennifer Evans Dr Steven Foster Dr Hannah Mitchell Dr Lisa McFetridge
Funder:	Public Health Agency – Research & Development Grant – Reference: COM/5596/20
Study Design:	Prospective longitudinal seroprevalence study
Study Participants:	Healthy children between 2 to 15 years from the United Kingdom.
Sample Size:	1000 children from five UK sties (Belfast, Cardiff, Glasgow, London and Manchester).
Study Period:	6 months from enrolment
Primary Objective:	SARS-CoV-2 immunoglobulin M (IgM) and/or immunoglobulin G (IgG) at different time points.
Exploratory:	Store residual specimens for future research relating to COVID-19 in children.

Introduction

Background

Coronaviruses are non-segmented positive-stranded ribonucleic acid (RNA) viruses that primarily cause enzootic infections in mammals (2); however in recent years their transmission to humans has caused significant public health crises such as severe acute respiratory syndrome (SARS) in 2003 and the Middle East respiratory syndrome (MERS) in 2012 (3,4). The novel coronavirus identified in Hubei Province, China in late 2019 was recognised to be in the same genus as those causing SARS and MERS and was named by the International Committee on Taxonomy of Viruses as SARS-CoV-2 in February 2020. The majority of patients infected with SARS-CoV-2 experience mild to moderate symptoms, but a proportion develop rapidly progressive acute respiratory distress syndrome and multi-organ failure (5,6). In February 2020 the World Health Organisation (WHO) named the disease caused by the SARS-CoV-2 virus COVID-19 (7).

Children with SARS-CoV-2 infection typically have a milder clinical course than adults and are less likely to require hospitalisation (8, 9). Whilst this is reassuring there have been rare reports of severe disease, specifically pneumonia, affecting children including a small number of deaths (two recorded deaths due to COVID-19 in the UK) (10, 11). More recently a disorder called “paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2” (PIMS-TS) has been described (12). This condition appears to be similar to Kawasaki disease. It is unclear if this is a novel condition or Kawasaki disease initiated by infection with SARS-CoV-2 (13). Whilst rare, PIMS-TS is of concern as some children have required admission to intensive care units (14).

It is unclear, currently, what proportion of children have been exposed to SARS-CoV-2 in the UK. As already described children have been relatively spared during the SARS-CoV-2 pandemic and overall they only account for 1.7% of reported cases in the USA (15), 1% of reported cases in the Netherlands (16) and 2% of reported cases in the UK (17). These reported confirmed cases are

unlikely to reflect the total number of exposed children due to the mild nature of COVID-19 in children. Infection survey pilots in the UK have shown no disparity in community cases of SARS-CoV-2 infection between adults and children (0.24% whole population and 0.30% under the age of 19) (18). A prospective seroprevalence study is therefore required to determine what proportion of children in the UK have been exposed to SARS-CoV-2 and what proportion, if any, have neutralising antibodies.

A better understanding of the current seroprevalence is vital for implementing and withdrawing social distancing measures. Social distancing measures such as closure of schools and playgrounds, cancelling routine paediatric clinics, and limited access to social care will have an effect on the physical and mental well-being of children (19-20). Deciding when normal services can be resumed is of paramount importance.

Study Design

This multicentre observational prospective cohort study will determine the seroprevalence of SARS-CoV-2 antibodies in healthy children. This study protocol has been written in conjunction with the SPIRIT 2013 Statement: Defining standard protocol items for clinical trials guideline (21) and will be reported adhering to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (22). Data from each centre will be collected over a period of 6 months from enrolment. A non-probability sampling method will be utilised.

Objectives

1. Report the seroprevalence of SARS-CoV-2 immunoglobulin M (IgM) and/or immunoglobulin G (IgG) antibodies in healthy children aged 2-15 years old at baseline 2 months after enrolment and 6 months after enrolment.
2. Determine if those antibodies are neutralising antibodies

Methods and Analysis

Setting

Approximately 1000 participants will be recruited from five centres (Belfast, Cardiff, Glasgow, London and Manchester) between May and July 2020.

Study Sites

- Belfast Health and Social Care Trust
- Cardiff and Vale University Health Board
- NHS Greater Glasgow and Clyde
- Public Health England (London)
- Manchester University NHS Foundation Trust

Participants

Children of healthcare workers who are aged between 2 and 15 years old.

Children currently receiving antibiotics, admitted to hospital within the last seven days, receiving oral immunosuppressive treatment or ever diagnosed with a malignancy will be excluded.

Informed consent

Informed consent will be obtained prior to inclusion. The parent is free to decline/withdraw consent at any time without providing a reason and without being subject to any resulting detriment. For children who turn 16 during the follow up period they will be invited to consent for the study again. If the young person declines consent they will be withdrawn from the study without being subject to any resulting detriment. Additional consent will be sought to store specimens for future research.

Assessments and procedures

The required assessments and procedures are outlined in Table 1. With the proposed pathway outlined in Figure 1. All children will undergo phlebotomy at baseline and at 2 months and 6 months after enrolment. Children with suspected COVID-19 (based on governmental testing guidance) will undergo molecular testing for SARS-CoV-2.

Phlebotomy

All blood sampling/phlebotomy will be carried out by experienced paediatric medical and nursing professionals. Topical anesthetic cream and distraction will be made available. A total of 5ml of blood will be taken from each individual. Serum plasma will be tested for Immunoglobulins G and M (IgG and IgM) to SARS-CoV-2. Testing will be carried out at Public Health England accredited laboratories using the Abbott SARS-CoV-2 IgG chemiluminescent microparticle immunoassay (23). As further assays are validated by Public Health England additional assays will be used including those for detection of IgM to SARS-CoV-2 and neutralizing antibodies.

Molecular Testing

Molecular testing for SARS-CoV-2 using real-time RT-QPCR (14) will be performed on oral/nasal and crevicular fluid swabs. This testing will be performed at accredited NHS hospital laboratories.

Symptom diaries

Participants that test positive for SARS-CoV-2 via real-time RT-PCR will be required to complete a symptom diary from the onset of their illness until resolution. (Copy of symptom diary is available in the online supplement).

Outcome Measures

Primary outcome measure:

- Presence of IgG and/or IgM antibodies to SARS-CoV-2 in serum plasma

Secondary outcome measures:

- SARS-CoV-2 infection confirmed by RT-QPCR testing of oral/nasal swabs and/or crevicular fluid.

Sample Size Justification

For each site to be able to detect a change in prevalence at each time-point of 10% (assuming an alpha of 0.05 and a beta of 0.2) then 171 children are required at each site. Allowing for at least a 10% drop out rate we estimate that each site will need to recruit approximately 200 patients. A total of 675 children are required from all sites to detect an overall change of 5% in seroprevalence across the entire population (assuming an alpha of 0.05 and a beta of 0.2). With five sites we anticipate recruiting approximately 1000 children. Participants will be recruited via advertisements circulated on hospital intranet and social media. Participants will receive a certificate acknowledging their contribution to the study.

Study Registration

This study was registered at https://www.clinicaltrials.gov (trial registration: NCT0434740) on the 07/04/2020 (last updated 27/05/20). At the time of registration no patients had been recruited to the study which opened on the 06/05/20. The end of the study will be the last study visit.

Patient and Public Involvement (PPI)

A PPI group comprising of parents and children coined the “Covid-Warriors” has been convened. They have contributed to the design of the study through online surveys and video discussions. The PPI group will be involved with producing the lay summary and the dissemination of final results.

Data Collection Plan

Data will be collected regarding the participant's age, sex, vaccination history and previous health. Data regarding potential predictors of seroconversion will be recorded including; known contact with individuals with COVID-19, contact with individuals who have been symptomatic and/or self-isolating, results of any diagnostic testing such as molecular testing/antibody testing.

Data Storage and management

Data will be recorded using a Case Report Form (CRF). Only anonymised non-personal data will be shared amongst the research team with personal data and linkage documentation remaining at the participating site under the care of the principle investigator. Data will be managed in accordance with General Data Protection Regulation (EU) 2016/679 (GDPR).

Statistical analysis plan

The study population will be described in terms of demographic characteristics with sex and median age. Simple descriptive statistics (total number and proportion) will be used to describe symptomology, vaccination status and household contacts and seroprevalence of SARS-CoV-2 antibodies. Adjusted probabilities for the presence of IgG and/or IgM antibodies and of SARS-CoV-2 infection will be reported, based on risk factors, using logistic regression models where appropriate. Analysis of the time to key events, such as seroconversion, will be reported using Kaplan-Meier estimates of the survivor function, including 95% confidence intervals, and proportional hazards or accelerated failure time models where appropriate. Incomplete datasets will be analysed using multiple imputation where possible.

Study Committees

Steering Committee

A core study team comprising of the chief investigator and principle investigators at each site and

statisticians have met and will meet regularly to monitor and report on the conduct of the study. Responsibilities include; agreeing the final study protocol, reviewing progress of the study and agreeing any changes to the protocol, data verification and publication of study reports.

Data Monitoring Committee

The principle investigators and statisticians will be meet after each clinic (baseline, two months and 6 months) to discuss the data, identify any missing data and to perform an interim analysis.

Adverse events

The study involves phlebotomy and swab testing only and no medicinal products are being administered. The likelihood of adverse events is low. All adverse events will be logged and reported the principle investigator at each site. Any serious adverse events will be reported to the chief investigator who will notify the study sponsor (Queen's University Belfast).

Protocol deviations and serious breaches

A deviation from the approved protocol will be recorded by the principle investigator at each site. Any serious breaches that could affect the safety or study participants much be reported to the chief investigator and sponsor. The sponsor will then determine if escalation to the research ethics committee is required.

Expenses and Benefits:

There is no reimbursement or benefit for participants taking part in this study. Children who participate in the study will receive a "COVID WARRIOR" certificate acknowledging their contribution.

Strengths and limitations

The strength of this study is that it is a large multi-centered prospective cohort seroprevalence study that will report the changing seroprevalence of SARS-CoV-2 antibodies over the coming months. The geographic spread of sites across the entire UK will provide detail on regional variations in seroprevalence and will provide data useful to devolved nations.

The study is limited in that it is not powered to detect very small changes in seroprevalence (less than 5%). The results may not be generalizable to the entire population as the included participants are all children of healthcare workers. Children of healthcare workers were however, chosen because the consent processes and preparation for phlebotomy will be easier amongst healthcare workers than the general population. The current social distancing restrictions make face-to-face consent discussions and the use of play therapists difficult. By recruiting children of healthcare workers those consent discussions are likely to be easier, due to a greater prior knowledge. Healthcare workers are also more likely to have a better insight into the study procedures and how to prepare children for phlebotomy.

Ethics and Dissemination

Publication plan

The final manuscripts will be published as pre-prints and for publication in high-impact medical journals and presented at medical conferences. The patient and public involvement group will be involved with the dissemination of the result findings and contribute to the lay summary. Authorship will be granted to those individuals who contribute in a meaningful way as judged by the study steering committee.

Potential risks/benefits

Additional distress from phlebotomy will be minimised by the use of experienced paediatric healthcare professionals and topical anesthetic creams. Parents can choose decline any procedure at any time. There are no benefits for the participants in this study.

Research Ethics & Governance

The London - Chelsea Research Ethics Committee (REC Reference - 20/HRA/1731) and the Belfast Health & Social Care Trust Research Governance (Reference 19147TW-SW) both provided favourable reviews. The study is sponsored by Queen's University Belfast. Amendments to the protocol will be submitted to the sponsor for categorization. Substantial amendments will be submitted for review by the Research Ethics Committee.

Contribution Statement

TW and SC were involved in conception and trial design. MC and TW were involved in drafting of the article. CW, MFD, DF, SL, ML, SF, JMK were involved in critical revision of the article for important intellectual content. LF and HM provided statistical expertise. RM and CMG informed and led on PPI group formation.

All authors have read and given final approval of the submitted manuscript.

Competing interests

James P McKenna holds share options in Hibergene Diagnostics Ltd, Sandyford, Dublin, Republic of Ireland. Dr. Fairley is non-executive director, advisory board member and shareholder in Hibergene Diagnostics Ltd, Sandyford, Dublin, Republic of Ireland.

Data Sharing Statement

All of the individual participant data collected during this study will be available (including data dictionaries) on the Queen's University Belfast data repository.

Funding

This work was supported by HSC R&D Division, Public Health Agency Ref: COM/5596/20. This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit result

REFERENCES

1.) Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497-506

2.) Schoeman D, Fielding BC. Coronavirus envelope protein: current knowledge. *Virol J*. 2019; 16: 69. https://doi.org/10.1186/s12985-019-1182-0

3.) Donnelly CA, Ghani AC, Leung GM, et al. Epidemiological determinants of spread of causal agent of severe acute respiratory syndrome in Hong Kong. Lancet 2003; 361: 1761–66. 3

4.) Cauchemez S, Fraser C, Van Kerkhove MD, et al. Middle East respiratory syndrome coronavirus: quantification of the extent of the epidemic, surveillance biases, and transmissibility. Lancet Infect Dis 2014; 14: 50–56.

5.) Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel CoronavirusInfected Pneumonia in Wuhan, China. JAMA 2020.

6.) Hui DSC, Zumla A. Severe Acute Respiratory Syndrome: Historical, Epidemiologic, and Clinical Features. Infect Dis Clin North Am 2019; 33: 869-889.

7.) WHO. Coronavirus disease 2019 (COVID-19): situation report—41. March 1, 2020. https://www.who.int/docs/default-source/ coronaviruse/situation-reports/20200301-sitrep-41-covid-19.pdf (accessed April 4, 2020).

8.) Livingston E, Bucher K. Coronavirus Disease 2019 (COVID-19) in Italy. JAMA [Internet]. 2020 Mar 17; Available from: http://jamanetwork.com/journals/jama/fullarticle/2763401

9.) Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiological Characteristics of 2143 Pediatric Patients With 2019 Coronavirus Disease in China. Pediatrics. 2020 Mar 16;e20200702.

10.) Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al. SARS-CoV-2 Infection in Children. New England Journal of Medicine. 2020 Mar 18;0 https://www.nejm.org/doi/full/10.1056/NEJMc2005073

11.) Provisional counts of the number of deaths registered in England and Wales, including deaths involving the coronavirus (COVID-19), by age, sex and region, in the latest weeks for which data are available week ending 15 May 2020. Statistical Bulletin. Office of National Statistics.https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsregisteredweeklyinenglandandwalesprovisional/latest Accessed 01/06/20

12.) Royal College of Paediatrics and Child Health. Guidance—Paediatric multisystem inflammatory syndrome temporally associated with COVID-19, 2020.

https://www.rcpch.ac.uk/resources/guidance-paediatricmultisystem-inflammatory-syndrome-temporally-associated-covid-19 (May 5, 2020)

13.) Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasakilike disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 2020; published online May 13. https://doi.org/10.1016/S0140-6736(20)31103-X.

14.) Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020; published online May 7. https://doi.org/10.1016/ S0140-6736(20)31094-1.

15.) Coronavirus Disease 2019 in Children—United States, February 12– April 2, 2020. MMWR Morb Mortal Wkly Rep 2020; 69: 422–26. 2

16.) Children and COVID-19. Amsterdam: National Institute for Public Health and the Environment (RIVM), 2020. https://www.rivm.nl/en/novelcoronavirus-covid-19/children-and-covid-19 (May 5, 2020).

17.) Docherty AB, Harrison EM, Green CA, et al. Features of 16,749 hospitalised UK patients with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol. medRxiv 2020; published online April 28. DOI:10.1101/ 2020.04.23.20076042 (preprint)

18.) Coronavirus (COVID-19) Infection Survey pilot: England, 10 May 2020 Estimates of people testing positive for the coronavirus (COVID-19) in England. Results from COVID-19 Infection Survey pilot. Statistical Bulletin. Office of National Statistics. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/coronaviruscovid19infectionsurvey/england10may2020 Accessed 01/06/20

19.) Cohen J, Kupferschmidt K. Countries test tactics in 'war' against COVID-19. Science 2020; 367: 1287–88.

20.) Wang G, Zhang Y, Zhao J, et al. Mitigate the effects of home confinement on children during the COVID-19 outbreak. Lancet 2020; published online March 4. https://doi.org/10.1016/ S0140–6736(20)30547-X.

21.) Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

22.) von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies**.** Lancet. 2007 Oct 20;370 (9596):1453-7.

23.) Evaluation of the Abbott SARS-CoV-2 IgG for the detection of anti-SARSCoV-2 antibodies. Public Health England. Published 18/05/20. https://www.gov.uk/government/publications/covid-19-laboratory-evaluations-of-serological-assays

Table 1: Assessment and procedures

Assessment/procedure	Healthy children
Consent discussion	In advance via telephone.
Assessment of eligibility criteria	In advance to attending initial clinic appointment via electronic consent form and discussion with researcher.
Phlebotomy	Baseline, 2 months, 6 months
RT-PCR Molecular Testing	When symptomatic
Data collection	Symptom diaries when unwell. Notes review if admitted.

Figure 1 Legend: Flow diagram outlining how interventions differ between participants who develop symptoms of COVID-19 vs those that remain asymptomatic.

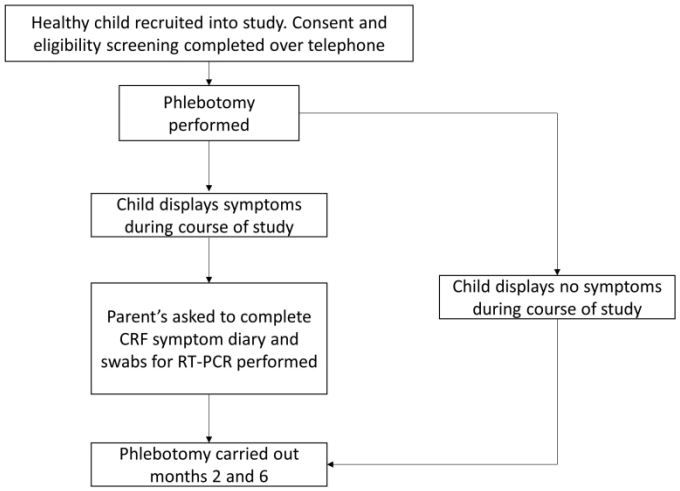

Figure 1: Clinical Pathway

338x190mm (300 x 300 DPI)

Study ID: [ ]

Symptoms:

Tick all that apply (if you need additional days please use a second diary)

Symptom	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day11	Day12	Day 13	Day 14
Fever														
Shivers/chills														
Cold hands/feet														
Abnormal colour														
Reduced activity														
Lethargy														
Unsettled/crying														
Headache														
Photophobia														
Reduced eating/drinking														
Rash														
Sore ears														
Sore throat														
Diarrhoea														
Vomiting														
Abdominal cramps/pain														
Abdominal														
Cough														
Runny nose														
Wheeze														
Loss of smell/taste														
Other (state)														
Other (state)														
Other (state)														
Other (state)														

Symptom Diary

How severe was the illness on each day (put a number in for each day)

- 1- My child is not affected very much and is able to carry on as normal
- 2- My child is slightly affected but I am not concerned
- 3- I have some concern but I do not plan to see a doctor or nurse
- 4 -I have some concern and I plan to see a doctor or nurse but not at the hospital
- 5 –I have concerns and have taken my child to hospital

Severity	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**
(1 to 5)								

What should I do if I think my child has coronavirus or is unwell?

If you're child is unwell for any reason with symptoms such as a fever, cough or coryza then you can arrange for a coronavirus test and study blood test by calling [Enter phone number here]. If you're concerned that your child may need to see a doctor then you should speak with your own GP surgery or call 999 (for emergencies). For further details on coronavirus and what to do if someone in your household is unwell can be found via the link below.

https://www.publichealth.hscni.net/news/covid-19-coronavirus#what-should-i-do-if-i-think-i-have-coronavirus

Reporting checklist for protocol of a clinical trial.

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Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 8
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Page 5
Protocol version	#3	Date and version identifier	Page 5
Funding	#4	Sources and types of financial, material, and other support	Page 14
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	Page 18
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	Page 5
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Page 14

Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Page 12
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 6/7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	Page 6
Objectives	#7	Specific objectives or hypotheses	Page 7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	Page 7

Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 8
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Pages 8/9
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	N/A – Having phlebotomy. If not possible then will not be performed.
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for	Page 12

		monitoring adherence (eg, drug tablet return; laboratory tests)	
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Pages 9
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and tme point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 10
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Pages 10

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 10
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care	N/A

		providers, outcome assessors, data analysts), and how	
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 10
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 10

Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Pages 10/11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 10
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 10
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in	Page 12

		the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A (observational)
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 12
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 12 (No additional steps beyond committees already discussed. Observational study)
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	Page 14
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant	Page 14

		parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Page 8
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 11
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 18
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 11
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A

Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 14
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	Page 14
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 14
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Included:
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Included:

BMJ Open

Seroprevalence of SARS-CoV-2 antibodies in children of healthcare workers- A prospective multicentre cohort study protocol

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Seroprevalence of SARS-CoV-2 antibodies in children of healthcare workers- A prospective multicentre cohort study protocol

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Abstract

Background:

A novel coronavirus SARS-CoV-2 has been responsible for a worldwide pandemic. Children typically have very mild, or no, symptoms of infection. This makes estimations of seroprevalence in children difficult. Research is therefore required to determine the seroprevalence of SARS-CoV-2 antibodies in children. The primary objective of this study is to report the seroprevalence of SARS-CoV-2 Immunoglobulin M (IgM) and/or Immunoglobulin G (IgG) antibodies in healthy children at baseline, two months and six months. This is the only longitudinal UK study of seroprevalence in an exclusively paediatric population. Determining the changing seroprevalence is of vital public health importance and can help inform decisions around the lifting of paediatric specific social distancing measures such as school closures and the cancellation of routine paediatric hospital services.

Methods and Analysis:

1000 healthy children of healthcare workers aged between 2 and 15 years will be recruited from five UK sites (Belfast, Cardiff, Glasgow, London and Manchester). The children will undergo phlebotomy at baseline, 2 months and 6 months to measure IgM and/or IgG positivity to SARS-CoV-2. A sample size of 675 patients is required to detect a 5% change in seroprevalence at each time point assuming an alpha of 0.05 and a beta of 0.2. Adjusted probabilities for the presence of IgG and/or IgM antibodies and of SARS-CoV-2 infection will be reported using logistic regression models where appropriate.

Ethics and Dissemination:

Ethical approval was obtained from the London - Chelsea Research Ethics Committee (REC Reference - 20/HRA/1731) and the Belfast Health & Social Care Trust Research Governance (Reference 19147TW-SW). Results of this study will be made available as pre-prints and submitted for publication in peer-reviewed journals.

Registration

Trial Registration: NCT0434740

Keywords

Children, COVID-19, seroprevalence, SARS-CoV-2

Word Count: 1832

Article Summary

- This study is a large multicentre cohort study concerning the seroprevalence of IgG and/or IgM antibodies to Sars-CoV-2 in children over 2 years of age.
- This is the only longitudinal UK study of seroprevalence in exclusively paediatric populations, and will provide important information which could help guide public health policy related to the COVID-19 pandemic.
- The geographic spread of sites across all four nations of the UK will provide detail of regional variation of seroprevalence.
- Whilst chosen for practical reasons the inclusion of only children of healthcare workers may limit the generalisability of this study to the whole population.
- A limitation of this study is that it is not powered to detect very small (less than 5%) changes in seroprevalence

Introduction

Background

Coronaviruses are non-segmented positive-stranded ribonucleic acid (RNA) viruses that primarily cause enzootic infections in mammals (1, 2); however in recent years their transmission to humans has caused significant public health crises such as severe acute respiratory syndrome (SARS) in 2003 and the Middle East respiratory syndrome (MERS) in 2012 (3,4). The novel coronavirus identified in Hubei Province, China in late 2019 was recognised to be in the same genus as those causing SARS and MERS and was named by the International Committee on Taxonomy of Viruses as SARS-CoV-2 in February 2020. The majority of patients infected with SARS-CoV-2 experience mild to moderate symptoms, but a proportion develop rapidly progressive acute respiratory distress syndrome and multi-organ failure (5,6). In February 2020 the World Health Organisation (WHO) named the disease caused by the SARS-CoV-2 virus COVID-19 (7).

Children with SARS-CoV-2 infection typically have a milder clinical course than adults and are less likely to require hospitalisation (8, 9). Whilst this is reassuring there have been rare reports of severe disease, specifically pneumonia, affecting children including a small number of deaths (two recorded deaths due to COVID-19 in the UK) (10, 11). More recently a disorder called “paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2” (PIMS-TS) has been described (12). This condition appears to be similar to Kawasaki disease. It is unclear if this is a novel condition or Kawasaki disease initiated by infection with SARS-CoV-2 (13). Whilst rare, PIMS-TS is of concern as some children have required admission to intensive care units (14).

It is unclear, currently, what proportion of children have been exposed to SARS-CoV-2 in the UK. As already described children have been relatively spared during the SARS-CoV-2 pandemic and overall they only account for 1.7% of reported cases in the USA (15), 1% of reported cases in the

Netherlands (16) and 2% of reported cases in the UK (17). These reported confirmed cases are unlikely to reflect the total number of exposed children due to the mild nature of COVID-19 in children. Infection survey pilots in the UK have shown no disparity in community cases of SARS-CoV-2 infection between adults and children (0.24% whole population and 0.30% under the age of 19) (18). A prospective seroprevalence study is therefore required to determine what proportion of children in the UK have been exposed to SARS-CoV-2, how long antibodies persist for and the symptoms associated with COVID-19 in healthy children.

A better understanding of the current seroprevalence is vital for implementing and withdrawing social distancing measures. Social distancing measures such as closure of schools and playgrounds, cancelling routine paediatric clinics, and limited access to social care will have an effect on the physical and mental well-being of children (19-20). Deciding when normal services can be resumed is of paramount importance.

Study Design

This multicentre observational prospective cohort study will determine the seroprevalence of SARS-CoV-2 antibodies in healthy children. This study protocol has been written in conjunction with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (21). Data from each centre will be collected over a period of 6 months from enrolment. A non-probability sampling method will be utilised.

Objectives

1. Report the seroprevalence of SARS-CoV-2 immunoglobulin M (IgM) and/or immunoglobulin G (IgG) antibodies in healthy children aged 2-15 years old at baseline 2 months after enrolment and 6 months after enrolment.
2. Determine if antibodies persist at 2 months and 6 months.

3. Report the symptoms associated with COVID-19 in children.

Methods and Analysis

Setting

Approximately 1000 participants will be recruited from five centres (Belfast, Cardiff, Glasgow, London and Manchester) between May and July 2020.

Study Sites

- Belfast Health and Social Care Trust
- Cardiff and Vale University Health Board
- NHS Greater Glasgow and Clyde
- Public Health England (London)
- Manchester University NHS Foundation Trust

Participants

Children of healthcare workers who are aged between 2 and 15 years old. For the purpose of this study, a healthcare worker is defined as an employee of the National Health Service. Healthcare workers will be categorized based on their role and if that role involves patient facing activities or not. A group of approximately 200 non-clinical and non-patient facing staff such as managerial staff and secretaries will be included to provide a comparison to clinical staff and improve the generalizability of the results. Participants will be recruited from each participating NHS organisation using internal intranet advertisements and email circulars.

Children currently receiving antibiotics, admitted to hospital within the last seven days, receiving oral immunosuppressive treatment or ever diagnosed with a malignancy will be excluded.

Informed consent

Informed consent will be obtained prior to inclusion including assent from the child. The parent/child is free to decline/withdraw consent at any time without providing a reason and without being subject to any resulting detriment. For children who turn 16 during the follow up period they will be invited to consent for the study again. If the young person declines consent they will be withdrawn from the study without being subject to any resulting detriment. Additional consent will be sought to store specimens for future research.

Assessments and procedures

The required assessments and procedures are outlined in Table 1. With the proposed pathway outlined in Figure 1. All children will undergo phlebotomy at baseline and at 2 months and 6 months after enrolment. Children with suspected COVID-19 (based on governmental testing guidance) will undergo molecular testing for SARS-CoV-2.

Phlebotomy

All blood sampling/phlebotomy will be carried out by experienced paediatric medical and nursing professionals. Topical anesthetic cream and distraction will be made available. A total of 5ml of blood will be taken from each individual.

Antibody testing

Serum and/or plasma will be tested for Immunoglobulins G and M (IgG and IgM) to SARS-CoV-2. Testing will be carried out at Public Health accredited laboratories using a range of assays including (but not limited to):

- Nuncleocapsid assays - (Abbott and Roche SARS-CoV-2 IgG assays)
- Spike protein assays – (DiaSorin LIAISON SARSCoV-2 S1/S2 IgG)

Assay results will be reported as total titers and as a binary positive/negative based on manufacturers suggested cut-off values.

Molecular Testing

Molecular testing for SARS-CoV-2 using real-time RT-QPCR is available for all children at all sites via existing testing strategies as part of the UK response to the COVID-19 pandemic (14). If a study participant develops symptoms of COVID-19 they will be asked to arrange a molecular test and feedback the result to the research team. This approach ensures that any participant-testing positive for SARS-CoV-2 is included in the Public Health response.

Data Collection

Study data will be collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools (22). Participants and their parents will provide information relating to illness episodes, suspected household exposure to SARS-CoV-2 and the outcome of any molecular testing at each clinic appointment. Participants will be provided with electronic symptom diaries to record any illness episodes relating to possible COVID-19 . Participants will be asked to record from their perceived first day of illness until their perceived last day of illness. In all instances, symptoms of illness episodes will be recorded prior to antibody test results being disclosed to minimise recall bias. (Copy of symptom diaries and RedCap case report forms are available in the online supplement files 1&2).

Outcome Measures

Primary outcome measure:

- Presence of IgG and/or IgM antibodies to SARS-CoV-2 in serum plasma

Secondary outcome measures:

- SARS-CoV-2 infection confirmed by RT-QPCR testing of oral/nasal swabs and/or crevicular fluid.

Sample Size Justification

For each site to be able to detect a change in prevalence at each time-point of 10% (assuming an alpha of 0.05 and a beta of 0.2) then 171 children are required at each site. Allowing for at least a 10% drop out rate we estimate that each site will need to recruit approximately 200 patients. A total of 675 children are required from all sites to detect an overall change of 5% in seroprevalence across the entire population (assuming an alpha of 0.05 and a beta of 0.2). With five sites we anticipate recruiting approximately 1000 children. Participants will be recruited via advertisements circulated on hospital intranet and social media. Participants will receive a certificate acknowledging their contribution to the study.

Study Registration

This study was registered at https://www.clinicaltrials.gov (trial registration: NCT0434740) on the 15/04/2020 (last updated 27/05/20). At the time of registration no patients had been recruited to the study which opened on the 06/05/20. The end of the study will be the last study visit.

Patient and Public Involvement (PPI)

A PPI group comprising of parents and children coined the "Covid-Warriors" has been convened. They have contributed to the design of the study through online surveys and video discussions. The PPI group will be involved with producing the lay summary and the dissemination of results.

Data Collection Plan

Data will be collected regarding the participant's age, sex, vaccination history and previous health.

Data regarding potential predictors of seroconversion will be recorded including; known contact with individuals with COVID-19, contact with individuals who have been symptomatic and/or self-isolating, results of any diagnostic testing such as molecular testing/antibody testing.

Data Storage and management

Only anonymised non-personal data will be shared amongst the research team with personal data and linkage documentation remaining at the participating site under the care of the principle investigator. Data will be managed in accordance with General Data Protection Regulation (EU) 2016/679 (GDPR).

Data Sharing

All of the individual participant data collected during this study will be available (including data dictionaries) on the Queen's University Belfast data repository.

Statistical analysis plan

The study population will be described in terms of demographic characteristics with sex, median age and healthcare role of parents. Simple descriptive statistics (total number and proportion) will be used to describe symptomology, vaccination status and household contacts and seroprevalence of SARS-CoV-2 antibodies. Logistic regression modelling will be used to estimate the probability of the presence of SARS-CoV-2 antibodies, adjusting for factors including demographic features (age, gender) and symptomology (such as fever, cough, fatigue), that are deemed statistically significant.

Study Committees

Steering Committee

A core study team comprising of the chief investigator and principle investigators at each site and statisticians have met and will meet regularly to monitor and report on the conduct of the study.

Responsibilities include; agreeing the final study protocol, reviewing progress of the study and agreeing any changes to the protocol, data verification and publication of study reports.

Data Monitoring Committee

The principle investigators and statisticians will be meet after each clinic (baseline , two months and 6 months) to discuss the data, identify any missing data and to perform an interim analysis.

Adverse events

The study involves phlebotomy and swab testing only and no medicinal products are being administered. The likelihood of adverse events is low. All adverse events will be logged and reported the principle investigator at each site. Any serious adverse events will be reported to the chief investigator who will notify the study sponsor (Queen's University Belfast).

Protocol deviations and serious breaches

A deviation from the approved protocol will be recorded by the principle investigator at each site. Any serious breaches that could affect the safety or study participants much be reported to the chief investigator and sponsor. The sponsor will then determine if escalation to the research ethics committee is required.

Expenses and Benefits:

There is no reimbursement or benefit for participants taking part in this study. Children who participate in the study will receive a "COVID WARRIOR" certificate acknowledging their contribution.

Strengths and limitations

The strength of this study is that it is a large multi-centered prospective cohort seroprevalence study that will report the changing seroprevalence of SARS-CoV-2 antibodies over the coming months. The geographic spread of sites across the entire UK will provide detail on regional variations in seroprevalence and will provide data useful to devolved nations.

The study is limited in that it is not powered to detect very small changes in seroprevalence (less than 5%). The results may not be generalizable to the entire population as the included participants are all children of healthcare workers. Children of healthcare workers were however, chosen because the consent processes and preparation for phlebotomy will be easier amongst healthcare workers than the general population. The current social distancing restrictions make face-to-face consent discussions and the use of play therapists difficult. By recruiting children of healthcare workers those consent discussions are likely to be easier, due to a greater prior knowledge. Healthcare workers are also more likely to have a better insight into the study procedures and how to prepare children for phlebotomy.

Ethics and Dissemination

Publication plan

The final manuscripts will be published as pre-prints and for publication in high-impact medical journals and presented at medical conferences. The patient and public involvement group will be involved with the dissemination of the result findings and contribute to the lay summary. Authorship will be granted to those individuals who contribute in a meaningful way as judged by the study steering committee.

Potential risks/benefits

Additional distress from phlebotomy will be minimised by the use of experienced paediatric

healthcare professionals and topical anesthetic creams. Parents can choose decline any procedure at any time. There are no benefits for the participants in this study.

Funding

This work was supported by HSC R&D Division, Public Health Agency Ref: COM/5596/20. This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit result

Research Ethics & Governance

The London - Chelsea Research Ethics Committee (REC Reference - 20/HRA/1731) and the Belfast Health & Social Care Trust Research Governance (Reference 19147TW-SW) both provided favourable reviews. The study is sponsored by Queen's University Belfast. Amendments to the protocol will be submitted to the sponsor for categorization. Substantial amendments will be submitted for review by the Research Ethics Committee.

REFERENCES

1.) Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497-506

2.) Schoeman D, Fielding BC. Coronavirus envelope protein: current knowledge. *Virol J*. 2019; 16: 69. https://doi.org/10.1186/s12985-019-1182-0

3.) Donnelly CA, Ghani AC, Leung GM, et al. Epidemiological determinants of spread of causal agent of severe acute respiratory syndrome in Hong Kong. Lancet 2003; 361: 1761–66. 3

4.) Cauchemez S, Fraser C, Van Kerkhove MD, et al. Middle East respiratory syndrome coronavirus: quantification of the extent of the epidemic, surveillance biases, and transmissibility. Lancet Infect Dis 2014; 14: 50–56.

5.) Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel CoronavirusInfected Pneumonia in Wuhan, China. JAMA 2020.

6.) Hui DSC, Zumla A. Severe Acute Respiratory Syndrome: Historical, Epidemiologic, and Clinical Features. Infect Dis Clin North Am 2019; 33: 869-889.

7.) WHO. Coronavirus disease 2019 (COVID-19): situation report—41. March 1, 2020. https://www.who.int/docs/default-source/ coronaviruse/situation-reports/20200301-sitrep-41-covid-19.pdf (accessed April 4, 2020).

8.) Livingston E, Bucher K. Coronavirus Disease 2019 (COVID-19) in Italy. JAMA [Internet]. 2020 Mar 17; Available from: http://jamanetwork.com/journals/jama/fullarticle/2763401

9.) Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiological Characteristics of 2143 Pediatric Patients With 2019 Coronavirus Disease in China. Pediatrics. 2020 Mar 16;e20200702.

10.) Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al. SARS-CoV-2 Infection in Children. New England Journal of Medicine. 2020 Mar 18;0 https://www.nejm.org/doi/full/10.1056/NEJMc2005073

11.) Provisional counts of the number of deaths registered in England and Wales, including deaths involving the coronavirus (COVID-19), by age, sex and region, in the latest weeks for which data are available week ending 15 May 2020. Statistical Bulletin. Office of National Statistics.https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsregisteredweeklyinenglandandwalesprovisional/latest Accessed 01/06/20

12.) Royal College of Paediatrics and Child Health. Guidance—Paediatric multisystem inflammatory syndrome temporally associated with COVID-19, 2020.

https://www.rcpch.ac.uk/resources/guidance-paediatricmultisystem-inflammatory-syndrome-temporally-associated-covid-19 (May 5, 2020)

13.) Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasakilike disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 2020; published online May 13. https://doi.org/10.1016/S0140-6736(20)31103-X.

14.) Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020; published online May 7. https://doi.org/10.1016/ S0140-6736(20)31094-1.

15.) Coronavirus Disease 2019 in Children—United States, February 12– April 2, 2020. MMWR Morb Mortal Wkly Rep 2020; 69: 422–26. 2

16.) Children and COVID-19. Amsterdam: National Institute for Public Health and the Environment (RIVM), 2020. https://www.rivm.nl/en/novelcoronavirus-covid-19/children-and-covid-19 (May 5, 2020).

17.) Docherty AB, Harrison EM, Green CA, et al. Features of 16,749 hospitalised UK patients with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol. medRxiv 2020; published online April 28. DOI:10.1101/ 2020.04.23.20076042 (preprint)

18.) Coronavirus (COVID-19) Infection Survey pilot: England, 10 May 2020 Estimates of people testing positive for the coronavirus (COVID-19) in England. Results from COVID-19 Infection Survey pilot. Statistical Bulletin. Office of National Statistics. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/coronaviruscovid19infectionsurvey/england10may2020 Accessed 01/06/20

19.) Cohen J, Kupferschmidt K. Countries test tactics in 'war' against COVID-19. Science 2020; 367: 1287–88.

20.) Wang G, Zhang Y, Zhao J, et al. Mitigate the effects of home confinement on children during the COVID-19 outbreak. Lancet 2020; published online March 4. https://doi.org/10.1016/S0140–6736(20)30547-X.

21.) von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies**.** Lancet. 2007 Oct 20;370 (9596):1453-7.

22.) Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform [Internet]. 2009 Apr [cited 2019 Oct 17];42(2):377–81. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18929686

Authors Statement

TW and SC were involved in conception and trial design. MC and TW were involved in drafting of the article. CW, JAM, MDS, DF, SL, ML, SF, JMcK, JE, PM and GRS were involved in critical revision of the article for important intellectual content. LMcF and HM provided statistical expertise. RM, KF and CMcG informed and led on PPI group formation.

All authors have read and given final approval of the submitted manuscript.

Competing interests

James P McKenna holds share options in Hibergene Diagnostics Ltd, Sandyford, Dublin, Republic of Ireland. Dr. Fairley is non-executive director, advisory board member and shareholder in Hibergene Diagnostics Ltd, Sandyford, Dublin, Republic of Ireland.

Table 1: Assessment and procedures

Assessment/procedure	Healthy children
Consent discussion	In advance via telephone.
Assessment of eligibility criteria	In advance to attending initial clinic appointment via electronic consent form and discussion with researcher.
Phlebotomy	Baseline, 2 months, 6 months
RT-PCR Molecular Testing	When symptomatic arranged through current Public Health testing. Participants to feedback results to researchers.
Data collection	Symptom diaries when unwell and additional data collection at clinics via RedCap data capture tools. Notes review if admitted.

Figure 1: Clinical Pathway for children enrolled in the study.

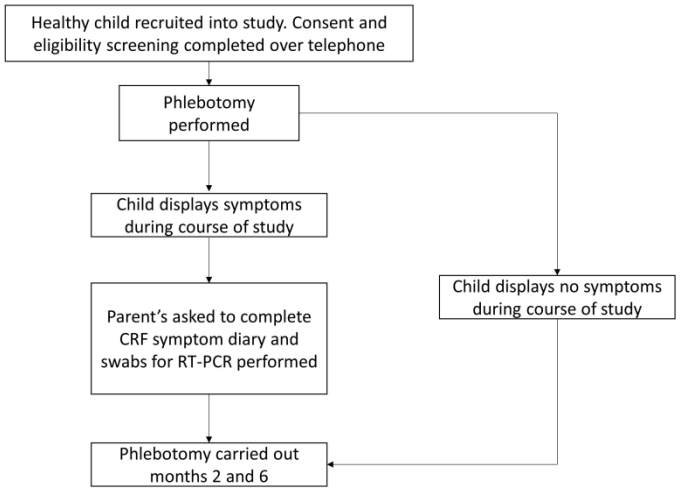

Figure 1: Clinical Pathway

338x190mm (300 x 300 DPI)

Version 4.0
08/04/2020
IRAS ID: 282617

Symptom Diary

Study ID: [Generated automatically or entered by researcher]

Symptoms:

Tick all that apply (if you need additional days please use a second diary)

Symptom	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
Fever								
Shivers/chills								
Cold hands/feet								
Abnormal colour								
Reduced activity								
Lethargy/sleeping more than usual								
Unsettled/crying more than usual								
Headache								
Photophobia (dislike of lights)								
Reduced eating/drinking								
Rash								
Sore ears								
Sore throat								
Diarrhoea								
Vomiting								
Abdominal cramps/pain								
Abdominal bloating/distension								
Cough								
Runny nose								
Wheeze								

Version 4.0
08/04/2020
IRAS ID: 282617

Symptom Diary

How severe was the illness on each day (put a number in for each day)

- 1- My child is not affected very much and is able to carry on as normal
- 2- My child is slightly affected but I am not concerned
- 3- I have some concern but I do not plan to see a doctor or nurse
- 4 -I have some concern and I plan to see a doctor or nurse but not at the hospital
- 5 –I have concerns and have taken my child to hospital

Severity	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**
(1 to 5)								

What should I do if I think my child has coronavirus or is unwell?

If you're child is unwell for any reason with symptoms such as a fever, cough or coryza then you can arrange for a coronavirus test and study blood test by calling [Enter phone number here]. If you're concerned that your child may need to see a doctor then you should speak with your own GP surgery or call 999 (for emergencies). For further details on coronavirus and what to do if someone in your household is unwell can be found via the link below.

https://www.publichealth.hscni.net/news/covid-19-coronavirus#what-should-i-do-if-i-think-i-have-coronavirus

RAPID-19 first follow up

Please use this form to collect data for patients attending their first follow up appointment after being enrolled in the RAPID-19 study.

All fields must be completed prior to submission

Study ID

Participant ID _____

Symptoms & diagnosis

To the best of your memory, did the child have any illnesses which you suspected were due to COVID BEFORE enrolment?

- ◯ Yes
- ◯ No

In regards to that illness BEFORE enrolment, please select whether any of the following features were present

- ☐ No Symptoms
- ☐ Fever
- ☐ New cough
- ☐ New shortness of breath
- ☐ Sore throat
- ☐ Runny nose
- ☐ Myalgia
- ☐ Arthralgia
- ☐ Headache
- ☐ Vomiting
- ☐ Diarrhoea
- ☐ Anosmia
- ☐ Aguesia
- ☐ Skin rash
- ☐ Other

(Please select all that apply)

Please list any other clinical features of COVID infection SINCE enrolment here _____

Has the child had known or suspected COVID 19 infection SINCE enrolment?

- ☐ Yes - suspected by family, clinician not consulted
- ☐ Yes - suspected by clinician
- ☐ Yes - proven by testing
- ☐ No

Has the child had a diagnosis of PIMS-TS SINCE enrolment?

- ◯ Yes
- ◯ No

Please select whether any of the following features have been present SINCE enrolment	☐ No symptoms ☐ Fever ☐ New cough ☐ New shortness of breath ☐ Sore throat ☐ Runny nose ☐ Myalgia ☐ Arthralgia ☐ Headache ☐ Vomiting ☐ Diarrhoea ☐ Anosmia ☐ Aguesia ☐ Skin rash ☐ Other (Please select all that apply)
Please list any other clinical features of COVID infection SINCE enrolment here	_____
What was the date of onset of the first illness episode SINCE enrolment?	_____
Approximately how many days did this last?	_____
Did the family consult any healthcare services for this first illness episode?	☐ None ☐ 111 consultation or similar ☐ Pharmacist consultation ☐ GP consultation (virtual or face to face) ☐ Hospital consultation ☐ Other (Please select all that apply)
What was the nature of this other consultation?	_____
What was the highest care level required for this first illness episode?	◯ Managed at home ◯ Seen in hospital, no admission required ◯ Admitted to hospital inpatient ward ◯ Admitted to hospital high care area (HDU or PICU) ◯ Other
What was this other care area?	_____
Did the child have any further episodes of illness SINCE enrolment?	◯ Yes ◯ No
What was the date of onset of the second illness episode SINCE enrolment?	_____

Approximately how many days did this last?	_____
Did the family consult any healthcare services for this second illness episode?	☐ None ☐ 111 consultation or similar ☐ Pharmacist consultation ☐ GP consultation (virtual or face to face) ☐ Hospital consultation ☐ Other (Please select all that apply)
What was the nature of this other consultation?	_____
What was the highest care level required for this second illness episode?	◯ Managed at home ◯ Seen in hospital, no admission required ◯ Admitted to hospital inpatient ward ◯ Admitted to hospital high care area (HDU or PICU) ◯ Other
What was this other care area?	_____
Did the child have any further episodes of illness SINCE enrolment?	◯ Yes ◯ No
What was the date of onset of the third illness episode since enrolment?	_____
Approximately how many days did this last?	_____
Did the family consult any healthcare services for this third illness episode?	☐ None ☐ 111 consultation or similar ☐ Pharmacist consultation ☐ GP consultation (virtual or face to face) ☐ Hospital consultation ☐ Other (Please select all that apply)
What was the nature of this other consultation?	_____
What was the highest care level required for this third illness episode?	◯ Managed at home ◯ Seen in hospital, no admission required ◯ Admitted to hospital inpatient ward ◯ Admitted to hospital high care area (HDU or PICU) ◯ Other
What was this other care area?	_____
Did the child have any further episodes of illness SINCE enrolment?	◯ Yes ◯ No

What was the date of onset of the fourth illness episode since enrolment?	_____
Approximately how many days did this last?	_____
Did the family consult any healthcare services for this fourth illness episode?	☐ None ☐ 111 consultation or similar ☐ Pharmacist consultation ☐ GP consultation (virtual or face to face) ☐ Hospital consultation ☐ Other (Please select all that apply)
What was the nature of this other consultation?	_____
What was the highest care level required for this fourth illness episode?	◯ Managed at home ◯ Seen in hospital, no admission required ◯ Admitted to hospital inpatient ward ◯ Admitted to hospital high care area (HDU or PICU) ◯ Other
What was this other care area?	_____

Social contacts

Did anyone in the child's home have SUSPECTED COVID BEFORE enrolment?	◯ Yes ◯ No
Did anyone in the child's home have PROVEN COVID BEFORE enrolment?	◯ Yes ◯ No
What was the relationship of the child to this household contact?	_____
Has the child had contact with anyone who had suspected or proven COVID 19 infection SINCE enrolment?	◯ Yes ◯ No
What was the nature of this contact?	☐ Household family member ☐ Other family member ☐ School/other childcare or education establishment ☐ Other (Please select all that apply)
You said other - please describe	_____

Did this household member have suspected COVID, or COVID proven by swab?	◯ Clinically suspected ◯ Proven by swab
Did this other family member have suspected COVID, or COVID proven by swab?	◯ Clinically suspected ◯ Proven by swab
Did this school/educational establishment contact(s) have suspected COVID, or COVID proven by swab?	◯ Clinically suspected ◯ Proven by swab
Did this other contact(s) have suspected COVID, or COVID proven by swab?	◯ Clinically suspected ◯ Proven by swab
How strictly has the child been adhering to social distancing?	Not at all ——— Very strictly *(Place a mark on the scale above)*

COVID 19 swabbing

Has the child had any swabs taken for suspected COVID infection since enrolment?	◯ Yes ◯ No
What was the date of the first swab being taken?	_____
What was the result of the first swab?	◯ Positive ◯ Negative ◯ Indeterminate ◯ Not known by family
Did the child have any further swabs taken since enrolment?	◯ Yes ◯ No
What was the date of the second swab being taken?	_____
What was the result of the second swab?	◯ Positive ◯ Negative ◯ Indeterminate ◯ Not known by family
Did the child have any further swabs taken since enrolment?	◯ Yes ◯ No
What was the date of the third swab being taken?	_____
What was the result of the third swab?	◯ Positive ◯ Negative ◯ Indeterminate ◯ Not known by family
Did the child have any further swabs taken since enrolment?	◯ Yes ◯ No

What was the date of the fourth swab being taken?	_____
What was the result of the fourth swab?	◯ Positive ◯ Negative ◯ Indeterminate ◯ Not known by family
Did the child have any further swabs taken since enrolment?	◯ Yes ◯ No
What was the date of the fifth swab being taken?	_____
What was the result of the fifth swab?	◯ Positive ◯ Negative ◯ Indeterminate ◯ Not known by family

COVID 19 antibody testing

Has the child had antibody testing done outside of the RAPID 19 study since enrolment?	◯ Yes ◯ No
What was the date of the first antibody test?	_____
Was the first antibody test done via the NHS or privately?	◯ NHS ◯ Private
What was the result of the first antibody test?	◯ Positive ◯ Negative ◯ Not known
Has the child had any further antibody testing done outside of the RAPID 19 study since enrolment?	◯ Yes ◯ No
What was the date of the second antibody test?	_____
Was the second antibody test done via the NHS or privately?	◯ NHS ◯ Private
What was the result of the second antibody test?	◯ Positive ◯ Negative ◯ Not known
Has the child had any further antibody testing done outside of the RAPID 19 study since enrolment?	◯ Yes ◯ No
What was the date of the third antibody test?	_____
Was the third antibody test done via the NHS or privately?	◯ NHS ◯ Private

What was the result of the third antibody test?	◯ Positive ◯ Negative ◯ Not known

Vaccinations

Has the child received COVID 19 vaccine since enrolment?	◯ Yes ◯ No
What was the brand name of this vaccine?	_____ (If given as part of blinded RCT, please note that here)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 8
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Page 5
Protocol version	#3	Date and version identifier	Page 5
Funding	#4	Sources and types of financial, material, and other support	Page 14

Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	Page 18
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	Page 5
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Page 14
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Page 12
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 6/7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	Page 6
Objectives	#7	Specific objectives or hypotheses	Page 7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	Page 7

Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 8
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Pages 8/9
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	N/A – Having phlebotomy. If not possible then will not be performed.
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	Page 12
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Pages 9
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time	Page 10

		to event), method of aggregation (eg, median, proportion), and tme point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Pages 10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 10
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A

Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 10
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 10
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management	Pages 10/11

		procedures can be found, if not in the protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 10
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 10
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page 12
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A (observational)
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 12
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 12 (No additional steps beyond committees

			already discussed. Observational study)
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	Page 14
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	Page 14
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Page 8
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 11
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 18
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 11
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A

Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 14
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	Page 14
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 14
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Included:
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Included: